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Subchondral bone changes in hand and knee osteoarthritis detected by radiography

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Summary

Objective: To describe the changes in subchondral bone that occur with the onset and progression of osteoarthritis (OA) from macroradiographic assessment of patient's hand and knee joints.

Design: The high magnification and spatial resolution of macroradiography permits detailed anatomical changes to be detected in OA joints. Data on the subchondral cortical and cancellous bone, recorded from both cross-sectional and longitudinal studies of hand and knee OA, are described and discussed with reference to recent findings on the altered biomechanical properties of OA bone.

Results: In OA joints, both subchondral cortical plate and subjacent horizontal trabeculae increase in thickness early, prior to joint space narrowing (JSN). With progression, cortical plate sclerosis increased in 60% of OA hands and did not change in knee OA until JSN <1.5 mm in the medial diseased compartment. In knee OA, trabeculae, at sites of tibial subchondral sclerosis, increased in number and extent, changes that overlay a subarticular region that was osteoporotic. With cartilage loss, the articular surfaces in some knees appeared corrugated, and later, with bone-on-bone, the surfaces became flattened and deformed.

Conclusions: The weaker than normal bone within thickened subchondral cortical plate and trabeculae of OA joints leads, in advanced OA, to deformation of the articular surfaces and absorption of local stresses producing an effect similar to stress-shielding. This effect, it is suggested, results in the subarticular osteoporosis.

Key words: Osteoarthritis, Knee, Subchondral bone, Hand, Radiography.

Introduction

Imaging techniques permit the detection of anatomical changes that occur in the joints of patients with osteoarthritis (OA) and, importantly, monitor their evolution with disease progression. Two methods, scintigraphy and radiography, in particular are sensitive to detecting bony changes in joints. In scintigraphy, the degree of radioisotope uptake demonstrated in the 3-h bone scan image identifies the exposed mineral surface at sites of bone resorption or formation[1]. These scans reflect the level of bone remodeling activity at the time of the scan. By contrast, both standard and magnification radiography reveal anatomical changes in the joint that have occurred in the past. Standard radiography has a spatial resolution of approximately 0.2 mm, whereas magnification radiography or macroradiography has a spatial resolution of 25 to 50 μm[2]. The advantage of the latter, with its enhanced spatial resolution, is that it allows changes in bone to be detected at the histological level, and hence at an earlier stage of the disease than is possible by standard radiography[2].

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BONE FORMATION AND REMODELING IN OA

Evidence to suggest that changes in bone occur early in the development of OA came from bone scans following intravenous injection of isotope-labeled bone-seeking compounds. Early work by Hutton *et al*. showed that in hand OA, the increase in isotope concentration identified joints with OA prior to the onset of radiographic changes and was predictive of subsequent radiographic abnormalities of joint space loss and osteophytosis (Fig. 1)[3,4]. Additionally, it was found that in OA of the hand, joints showed variable levels of disease activity switching between an active and a quiescent phase[3,4]. A more detailed analysis of the distribution of the radiolabeled isotope and the changes in bony features in the early stages of hand OA showed that the increased uptake was associated with osteophyte growth and remodeling[5,6]. In later stages of the disease, the intensity of the scintigraphic scan at joints was also associated with increased subchondral sclerosis[7].

Radioisotope studies in knee OA confirmed the earlier work of Hutton *et al*.[3,4] on the predictive nature of this methodology in identifying joints likely to show progression[8,9]. In knee OA, the differing patterns of isotope uptake have been attributed to bone remodeling in different regions of the joint, with the suggestion that the tramline appearance of uptake on either side of the joint space corresponds to increased subchondral sclerosis[7]. Scintigraphic scans confirm the very early involvement of bone in

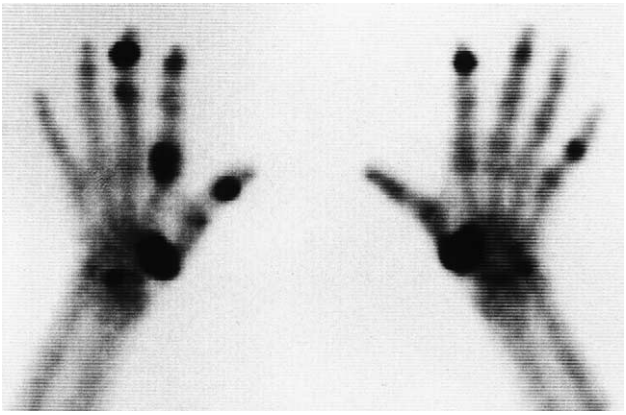

Fig. 1. Four-hour bone scan of patient's osteoarthritic hands. The increased isotope uptake at joints is associated with osteophyte growth and remodelling[5,6]. Some symmetry is observed between joints (e.g, 2nd and 3rd distal interphalangeal [DIP] and 1st carpal metacarpal [CMC]). Note also the variable level of disease activity, seen as difference in the degree of radioisotope uptake within the joints of the hand[3,4].

OA, prior to changes detected in standard radiographs. However, the poor spatial resolution of the scintigraphic image does not permit identification of the exact site of bony changes in OA joints.

What are the earliest bone changes in OA?

Radiography of OA joints in patients[10–14] has shown that the formation of osteophytes and subchondral sclerosis occurs many months before changes in articular cartilage thickness measured radiographically as joint space narrowing (JSN). These radiographic features are temporally separated primarily because the bone's rich blood supply permits it to respond relatively rapidly to altered conditions in the joint, whereas a physical loss of the articular cartilage, which occurs at a later stage of the disease, is necessary before JSN is detectable[10–14].

At which site are the earliest bony changes detected radiographically: in the subchondral region or at the articular margins of the synovial joint? The difficulty in determining the sequence of changes at these sites lies in not being able to identify the start of the disease or know the initiating or causative factor(s) for OA. A possible solution comes from retrospective studies in patients with post-traumatic anterior cruciate ligament (ACL) rupture. Radiographic changes in these patients are consistent with those of OA and occur in 60% to 90% of subjects 10 to 15 years after injury[15–20]. Patients with a tear in the cruciate ligament, isolated or combined with injuries to the collateral ligament or the menisci, show radiographic signs of OA at a younger age than patients with a meniscal tear only[21] and faster disease progression than patients with primary OA[18].

Since post-traumatic OA has the advantage that the beginning of the process can be identified by the date of the injury[21], a quantitative macroradiography cross-sectional study was undertaken to determine the sequence of appearance of the radiographic features relative to one another in patients with ACL rupture[14]. In particular, the study explored which of the bony features of subchondral cortical plate thickness, subchondral trabecular sclerosis, and osteophytosis occurred prior to or in association with changes in joint space width, measured as a surrogate for changes in articular cartilage thickness. Compared to the uninjured knee, ACL rupture led to thickening of subchondral horizontal trabeculae (as measured by a decrease in the values for fractal signature analysis [FSA]) in the medial tibial compartment of all injured knees, reaching significance ($P<0.01$) between 3 to 4 years after injury. Osteophytes were present in the same compartment in approximately 50% of injured knees by about the third year. No changes in joint space width (JSW) or subchondral cortical plate thickness were detected. Thus, in ACL-ruptured knees, the bony features of OA within the medial compartment of the tibia do not appear to be radiographically detectable until 3 to 4 years after the injury. Thickening of the horizontal subchondral trabeculae and the appearance of osteophytes occurred prior to subchondral cortical plate thickening and JSN. The pattern of changes detected in these patients with ACL-ruptured knees may be different from that in patients with idiopathic OA. The absence of a measurable increase in cortical plate thickness differed from our findings in patients with early knee OA[12,13,22], in whom the medial compartment tibial subchondral cortical plate was thicker than in a reference non-arthritic group[12]. This would suggest that there is coupling between cortical plate sclerosis and early changes in cartilage thickness. This observation is supported by data from both human hand and knee OA[10–12] and experimental animal work[1,23–26], including, for example, a study in cynomolgus macaques that suggested that there is a threshold subchondral plate thickness below which articular cartilage lesions do not occur[26].

The findings from radiographic assessment of changes in the subchondral region in OA hand and knee joints are described below. This region, composed of the zone of calcified cartilage, the cortical plate, and the subjacent cancellous bone region, appeared to change with the onset, as well as the progression, of OA in hand and knee joints.

Subchondral sclerosis in hand OA

In studies of hand OA, subchondral cortical plate thickness at study entry was significantly greater in all patients with hand OA than in subjects in a non-arthritic reference group[10,11,27]. Indeed, sclerosis was present in hands with very early OA[10,11,27], i.e., in those joints in which JSW measurements indicated cartilage swelling rather than loss[10,11], indicative of an altered cartilage biochemical status[28–30]. In longitudinal studies, cortical plate thickness in the wrist and hand increased significantly in two thirds of the patients, and in a third, it decreased. The decrease was attributed to localized peri-articular inflammation[10,11]. The distribution of increased cortical plate thickness in the wrist and hand joints was similar to the pattern of osteophyte formation[31] and corresponded to the distribution of force across the hand and wrist during normal activity (Table I)[11,27].

In approximately half the OA hands, advancement in the zone of calcified cartilage (ZCC) was seen at the joint's central convex articular surfaces (Fig. 2)[32,33]. The appearance of new ZCC steps 18 months later in a further 36% of patients' hands indicated that this feature was associated with disease progression[32]. The distribution of this feature at the interphalangeal and metacarpal joints suggests that its presence was associated with systemic rather than localized stress-related factors[33]. Further, the site of the advancing mineralized front at the middle of the convex

Table I
Compared to healthy non-arthritic reference group, the subchondral cortical plate thickness, measured from macroradiographs of patients with hand OA, was statistically significantly thicker. Sites of greatest increase in cortical plate thickness corresponded to the functional demand, and hence increased load, that occurred in the hand with different types of activity[11]

Greatest cortical plate thickness	Radiological site	Type of activity
Per joint	2nd distal interphalangeal joint	Pulp-pinch grip between finger and thumb
Per phalangeal ray	2nd and 3rd phalanges	Tripod finger action
Between hands	Dominant 2nd and 3rd >non-dominant 2nd and 3rd phalanges*	Handedness

* $P<0.045$ Wilcoxon matched paired test.

Fig. 2. Part of a macroradiograph of the metacarpophalangeal joints of a patient with osteoarthritis showing the advancement of the zone of calcified cartilage at the convex articular surfaces[32,33]. Advancement is seen to extend progressively further in the articular cartilage (arrow heads) from the 3rd to the 5th joint. Original magnification ×5, reproduced at ×2.8.

articular surfaces of the joints coincides with the presence of a larger number of vascular canals perforating the subchondral cortical plate at this site[34,35] than at the articular margins. The association between ZCC formation and vascular changes is further supported by the observation, in both patients and experimental animals, that the vascular invasion may be the result of lipid-related intraosseous venous thrombosis leading to focal bone ischemia followed by repair[36,37].

The step-like advancement of the ZCC into the body of the articular cartilage[38] has been observed histologically[39–41] and in post mortem examination of larger joints, such as the shoulder and hip[42]. Its presence in these joints appears to have a different function, acting as an intermediate stiffness layer between the articular cartilage and the subchondral bone[39,43,44]. At these sites, the normal undulating structure of the calcified cartilage interface with the overlying cartilage and the underlying subchondral bone transforms shear stresses into tensile and compressive stresses for which cartilage is better adapted[45].

Subchondral sclerosis in knee OA

SUBCHONDRAL CORTICAL PLATE

Femoral and tibial subchondral cortical plate thickness was well developed in OA knees with minimal or no joint space narrowing (Fig. 3)[12]. The cortical plate in these knees was significantly greater in the medial diseased than in the lateral compartment (Table II). The subchondral plate did not change in thickness during short-term longitudinal studies (18 to 24 months)[22], but was statistically significantly thicker in the tibia of knees with severe JSN (JSW $\leq$1.5 mm) than in knees with early to moderate disease[12], i.e., at a stage in which nearly all the articular cartilage had been lost and the subchondral plate had increased in thickness in response to the enhanced mechanical strains.

SUBCHONDRAL CANCELLOUS BONE

Significant changes in subchondral cancellous bone were detected in the medial diseased compartment of the

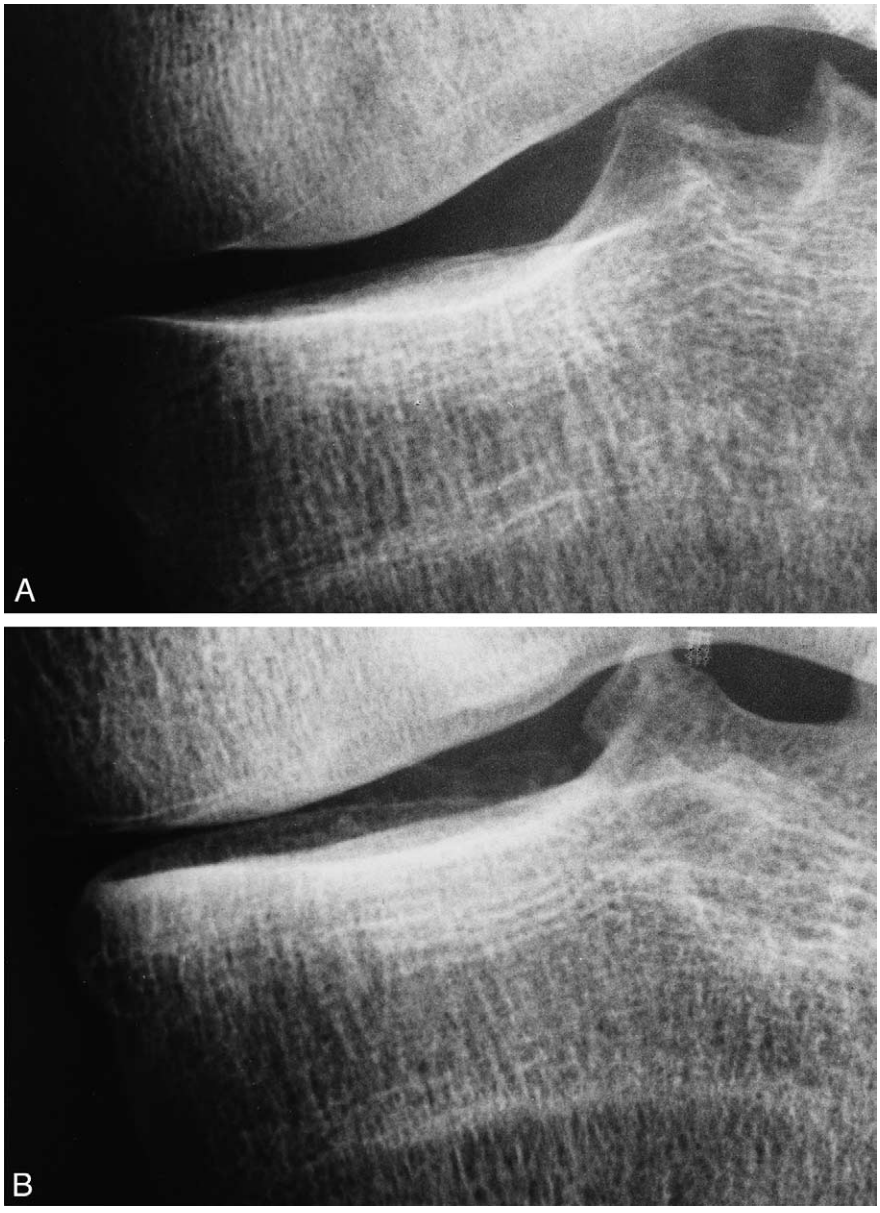

Fig. 3. Part of the macroradiographs of the medial compartment of osteoarthritic knees with (A) early disease, characterized by JSW >3 mm and (B) definite disease, characterized by JSW <3 mm. Radiograph of knee with definite disease (B) shows the increase in thickness of the subchondral cortical plate and subjacent horizontal trabeculae resulting in a ladder-like appearance. Original magnification ×5, reproduced ×3.2.

tibia in OA knee patients with early disease (JSW >3 mm)[13]. The technique of macroradiography[2], combined with a computerized textural analysis technique of Fractal Signature Analysis (FSA), which quantifies separately vertical and horizontal trabecular structures[46] within regions of interest in the OA knee, found that the earliest changes detected in patients was a significant increase in the thickness of the horizontal trabeculae ranging from 0.5 to 1.0 mm compared to patients in the healthy reference group[13]. In knees with more advanced OA and greater joint space loss, trabeculae were found to be significantly thicker and closer together than in knees from patients with less severe disease (Fig. 4)[13,47]. Changes in vertical trabeculae appeared at a later stage of the disease (JSW <3 mm) as an increase in their number attributed to trabecular fenestration and thinning[13,47]. No changes in the trabecular organization were found in the lateral non-diseased compartment of the proximal end of the tibia[13].

Thus, in patients with knee OA, both the subchondral cortical plate and subjacent horizontal trabeculae increased significantly in thickness prior to any measurable JSW loss[12,13]. Histologically, the new bone formed in OA is laid down rapidly as coarse fibred or woven-bone characteristic of sites of bone repair[48]. Biomechanical tests reveal that, compared with non-arthritic joints, the subchondral bone from OA patients is less stiff and dense, showing a greater porosity and a reduced mineral content[49] and is mechanically 'weaker.' This weakening of the subchondral

Table II
Mean (standard deviation [SD]) thickness of the subchondral cortical plate (mm) at the femoral and tibial articular surfaces in the medial tibiofemoral compartment of patients with medial compartment disease[12]

Knees‡	Number	Mean (SD) cortical plate thickness (mm) Femoral condyle	Tibial plateau
Reference group§	28	0.29 (0.07)	0.37 (0.06)
JSW >3 mm	36	0.54 (0.14)*	0.53 (0.11)*
JSW <3 mm	12	0.59 (0.21)	0.50 (0.09)
JSW <1.5 mm)	15	0.53 (0.21)	0.76 (0.16)†

‡Knees grouped according to minimum medial compartment joint space width (JSW) measurement: early disease (JSW >3 mm), definite disease (JSW <3 mm), and severe disease (JSW <1.5 mm).
§Reference group of healthy subjects.
*Significantly different from mean value for healthy reference group (P<0.0001), Mann–Whitney test).
†Significantly different from mean value for subgroup of patients with JSW >1.5 mm (P<0.0001), Mann–Whitney test).

bone is detected radiographically in a flattening of the femoral and tibial articular surfaces resulting in greater congruity of the articular elements (Fig. 5A). The tongue in groove corrugation on the corresponding femoral and tibial articular surfaces in this joint is a manifestation of a variable pattern of bone stiffness and weakness across the compartment. With complete loss of cartilage, the softened subchondral bone is further flattened and acquires greater articular congruence (Fig. 5B). Ultimately, in advanced stages of the disease, the articular surfaces become distorted and deformed with the collapse of the cancellous bone in the subarticular region leading to altered limb alignment and deformity (Fig. 6).

Periarticular and subarticular bone changes in knee OA

Localized osteopenia at the periarticular region is known to occur in the bone immediately adjacent to sites of osteophyte formation[51], and is coupled with the increased vascular supply associated with new bone formation. A more extensive region of osteoporosis in the subarticular bone, subjacent to the subchondral sclerosis (Fig. 7), has recently been quantified by bone densitometry[52]. Karvonen *et al.* found that the bone mineral density (BMD) in the subarticular cancellous bone was lower than normal, regardless of the BMD of the spine, and that the lower than normal BMD in knee OA appeared related to the radiographic changes at the joint[52]. Similar observations have also been made in experimental animals[23–26], in which subarticular osteoporosis occurred deep to the thickened cortical plate. It is possible that these osseous changes may be associated with the marrow lesions seen on magnetic resonance images (MRIs)[53] of painful knees. The changes appear to be associated with increased blood or fluid inside bone[53] possibly related to low grade inflammation, or to intraosseous hypertension due to poor venous drainage from the marrow[54].

The role of subchondral bone in OA

Osteoarthritis is a condition of the synovial joint that affects the osteochondral junction in which it is impossible

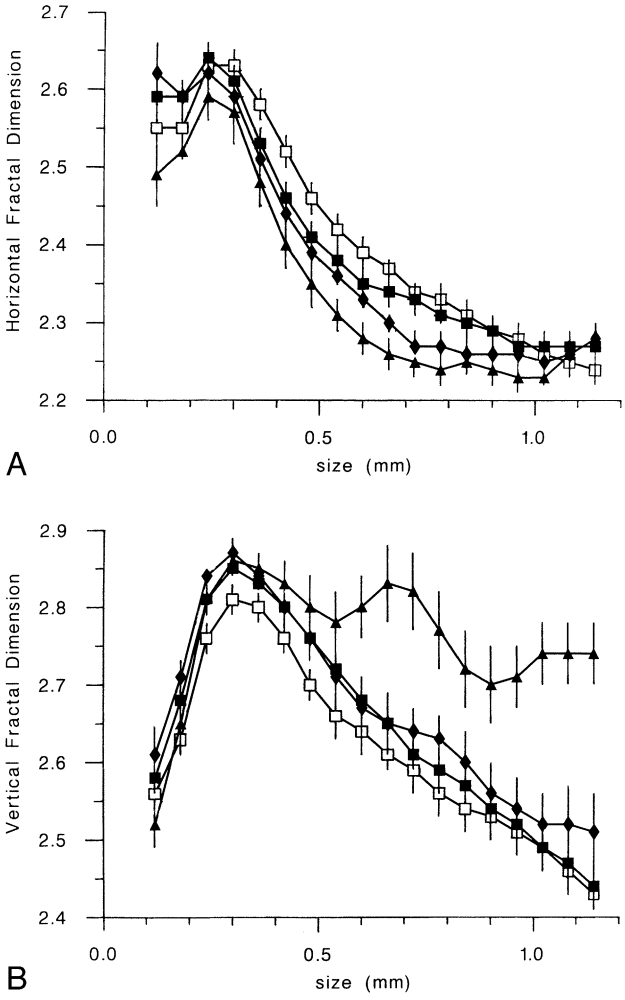

Fig. 4. The mean (SE) fractal signature for horizontal (A) and vertical (B) trabecular structures in the medial compartment of the tibia[13] of the reference group (□) and in OA knees with JSW >3 mm in both standing and tunnel views (■); OA knees with JSW <3 mm in both standing and tunnel views (♦), and OA knees with JSA <3 mm in the tunnel view only (▲). (Reproduced from the Annals of the Rheumatic Diseases 1996; 55: 752–753. [Reference 13] with permission from the BMJ Publishing Group.)

to separate the changes that occur in one tissue from those in the other[55]. The formation of bone in the region of subchondral sclerosis is an attempt at repair since histologically it is described as coarse fiber woven bone[48]. This type of bone is similar to callous bone formation at sites of fracture repair and at regions of rapid bone growth[56]. Biochemically, there is increased metabolism, both synthesis and degradation, of the subchondral bone collagen in OA, as well as changes to post-translational modifications, including increased lysine hydroxylation, changes in the nature of the cross-links between the polypeptide chains, and consequential decreased mineralization[57]. Recently, type I collagen homotrimer has been identified in osteoarthritic subchondral bone, in addition to the predominant type I heterotrimer found in normal bone, indicating a changed phenotypic expression of the osteoblasts[58]. Biomechanically, such changed collagen composition would be expected to alter the mechanical properties of bone, rendering it weaker as described above[49]. Thus, the

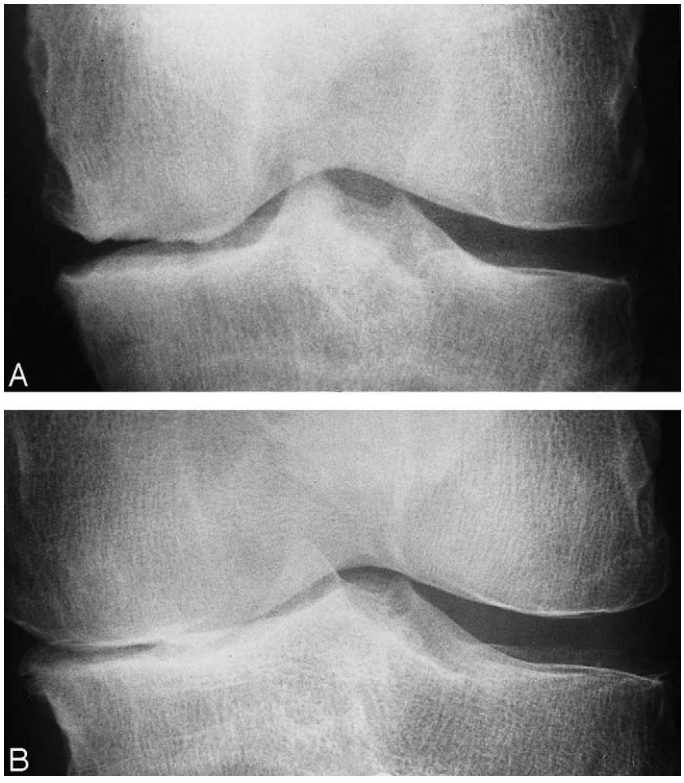

Fig. 5. (A) Radiograph of knee with osteoarthritis with medial compartment JSW >2 mm in the standing extended view. As described elsewhere[50], the joint space visible in the extended knee view does not correspond to articular cartilage thickness at the central region of the tibio-femoral joint, but to a 'gap' produced by the femoral condyle rolling forward onto the ridge at the anterior tibial rim. Importantly, observe in the medial compartment the marked subchondral sclerosis with tongue and groove corrugations on the femoral and tibial articular surfaces. The latter are consistent with the loss of cartilage in the flexed knee position. (B) The same OA knee as in (A) radiographed in the same view, 21 months later, showing marked articular cartilage loss in the medial compartment indicated by the narrowed joint space. With joint space loss, there is an increase in subchondral sclerosis, the articular surfaces appear flattened, and the corrugations visible in (A) are reduced or absent resulting in greater articular congruence, changes that are consistent with weak subchondral bone reported at OA joints[49].

formation of new bone, with its weaker biomechanical properties, in the subchondral sclerotic region of load-bearing joints accounts for a number of the anatomical changes observed in knee OA (Fig. 8).

The deformation and flattening of the articular contour that occurs in OA joints would have a two-fold effect. First, it would produce considerable stress within any cartilage remaining upon the articular surface, and second, it would increase the surface area of contact between the two articular elements. In turn this would improve load transmission across the joint, since bone is structurally better adapted to absorb forces over a larger than a small cross-sectional area[59]. These changes result in a greater congruity between joint surfaces and a consequent decrease in the mechanical stresses within articular structures[44]. The increased joint conformity and sclerosis within the subchondral cortical plate and trabeculae would lead to greater absorption of local stresses, reducing load transmission to the deeper subarticular region and resulting in a localized osteoporosis[52], similar to the effect of 'stress shielding' observed in the bone under metal prostheses[60,61]. In the lateral compartment of knees with medial compartment disease, the greater joint space loss in the later and associated valgus deformity would lead to joint subluxation and an unloading of the lateral compartment of the knee. Reduction in load transmission in this compartment would result in the onset of a disuse osteoporosis within the subchondral and subarticular cancellous bone.

The OA-related changes to the subchondral and subarticular cancellous bone, described above, can be summarized in the following hypothesis: that the weaker than normal bone in the subchondral cortical plate and trabeculae results in deformation of the joint surfaces and absorption of local stresses, resulting in a sub-articular osteoporosis detected as a reduction in BMD.

Further investigations are required to clarify the interplay between the biochemical, mechanical, and anatomical changes that take place within the subchondral and subarticular regions of bone in OA joints. At present, it would appear that it is the abnormal structure and mechanical properties of bone in the subchondral region that are not only integral to but may be responsible for disease progression in OA joints. Differences observed in the changes to the subchondral bone between hand and knee OA suggests that the stresses associated in weight-bearing joints are, in the long term, more likely to result in a failing joint, with the collapse of the articulation and subsequent need for surgical intervention. The overall findings described here support the concept that OA, or at least a major subset of this heterogeneous group of disorders, is a disorder of bone. Therapeutic strategies are required that are aimed

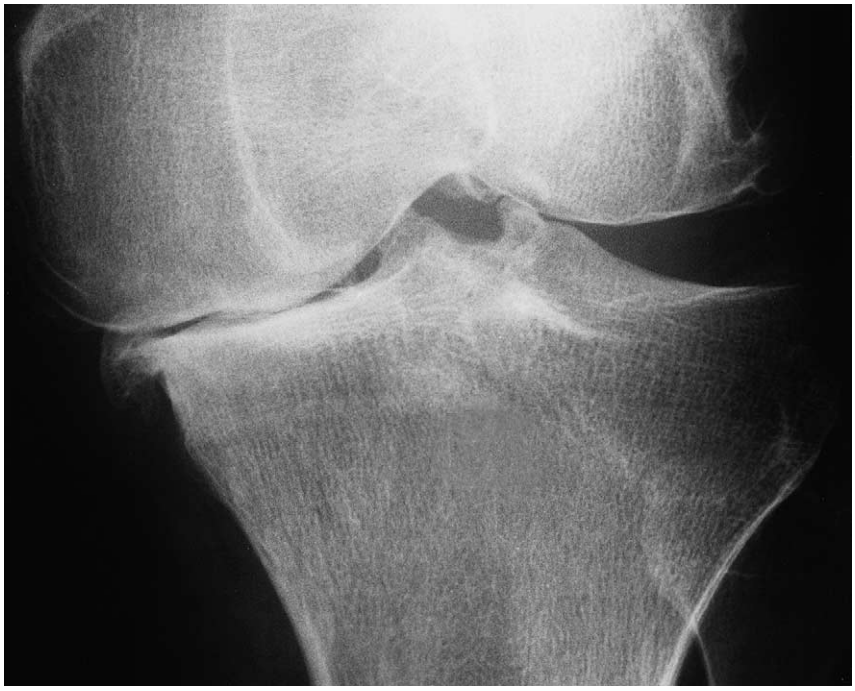

Fig. 6. Radiograph of an OA knee with severe disease showing the long-term effects of the weak subchondral bone[49] and sub-articular osteoporosis[38] resulting in the collapse of the medial compartment and joint mal-alignment.

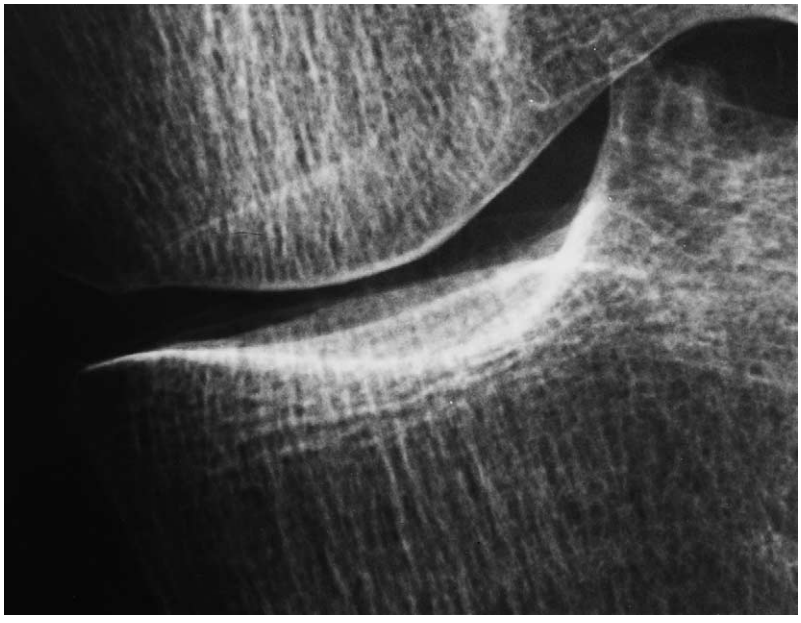

Fig. 7. Part of a macroradiograph of the medial compartment of an osteoarthritic knee with definite narrowing of the joint space showing the sub-articular region of osteoporosis lying below the subchondral sclerosis. The zone of reduced bone density extends out towards the osteophyte at the articular margin. Original magnification ×5, reproduced at ×3.5.

at preserving the normal healthy bone, at slowing down the process leading to the deposition within the subchondral region of the biomechanically weaker woven or repair bone, and at preventing the osteoporotic changes in the subarticular region. Were such treatment to have the effect of maintaining bone quality and hence the normal contour and shape of the articular surfaces, it is conceivable that this approach would preserve the patient's mobility for longer periods than therapies directed at preserving articular cartilage alone, since the latter is inevitably affected by the alterations in the subchondral bone described above.

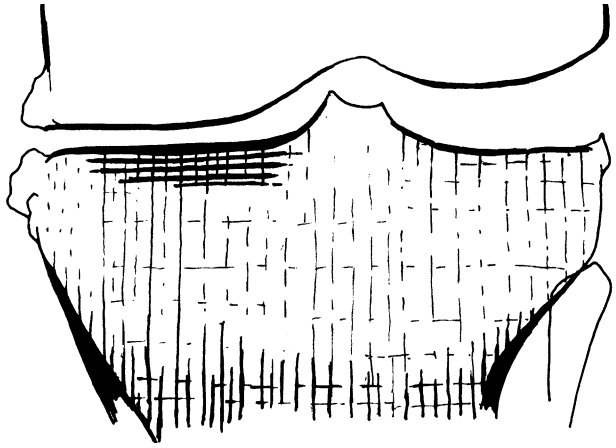

Fig. 8. Diagram of a knee with advanced OA illustrating the effect weight-bearing has on weaker than normal bone[49] within the region of thickened subchondral cortical plate and trabeculae. The articular surfaces deform and their contour is flattened, changes that lead to the absorption of local stresses within the subchondral region of sclerosis[44,59] and result in the formation of a sub-articular osteoporosis.

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